PATENT COOPERATION TREATY

From the
INTERNATIONAL SEARCHING AUTHORITY

To: 61

see form PCT/ISA/220

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY
(PCT Rule 43*bis*.1)

Date of mailing *(day/month/year)* see form PCT/ISA/210 (second sheet)	
Applicant's or agent's file reference see form PCT/ISA/220	**FOR FURTHER ACTION** See paragraph 2 below

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/CA2004/000948	28.06.2004	30.06.2003

International Patent Classification (IPC) or both national classification and IPC
C07C323/62, C07D231/12, C07D213/32, C07D235/06, C07D233/64, C07D211/20, C07D233/54, C07D213/83,

Applicant
MERCK FROSST CANADA & CO.

1. This opinion contains indications relating to the following items:

- ☒ Box No. I Basis of the opinion
- ☒ Box No. II Priority
- ☐ Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- ☐ Box No. IV Lack of unity of invention
- ☒ Box No. V Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- ☐ Box No. VI Certain documents cited
- ☐ Box No. VII Certain defects in the international application
- ☐ Box No. VIII Certain observations on the international application

2. **FURTHER ACTION**

If a demand for international preliminary examination is made, this opinion will usually be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA"). However, this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notifed the International Bureau under Rule 66.1*bis*(b) that written opinions of this International Searching Authority will not be so considered.

If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of three months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later.

For further options, see Form PCT/ISA/220.

3. For further details, see notes to Form PCT/ISA/220.

Name and mailing address of the ISA:	Authorized Officer
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WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/CA2004/000948

Box No. I Basis of the opinion

1. With regard to the **language**, this opinion has been established on the basis of the international application in the language in which it was field, unless otherwise indicated under this item.

   ☐ This opinion has been established on the basis of a translation from the original language into the following language , which is the language of a translation furnished for the purposes of international search (under Rules 12.3 and 23.1(b)).

2. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application and necessary to the claimed invention, this opinion has been established on the basis of:

   a. type of material:

   ☐ a sequence listing

   ☐ table(s) related to the sequence listing

   b. format of material:

   ☐ in written format

   ☐ in computer readable form

   c. time of filing/furnishing:

   ☐ contained in the international application as filed.

   ☐ filed together with the international application in computer readable form.

   ☐ furnished subsequently to this Authority for the purposes of search.

3. ☐ In addition, in the case that more than one version or copy of a sequence listing and/or table relating thereto has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.

4. Additional comments:

Box No. II Priority

1. ☒ The following document has not been furnished:

   ☒ copy of the earlier application whose priority has been claimed (Rule 43*bis*.1 and 66.7(a)).

   ☐ translation of the earlier application whose priority has been claimed (Rule 43*bis*.1 and 66.7(b)).

   Consequently it has not been possible to consider the validity of the priority claim. This opinion has nevertheless been established on the assumption that the relevant date is the claimed priority date.

2. ☐ This opinion has been established as if no priority had been claimed due to the fact that the priority claim has been found invalid (Rules 43*bis*.1 and 64.1). Thus for the purposes of this opinion, the international filing date indicated above is considered to be the relevant date.

3. Additional observations, if necessary:

Box No. V Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	1-11
	No:	Claims	
Inventive step (IS)	Yes:	Claims	3, 5, 6
	No:	Claims	1-2, 4, 7-11
Industrial applicability (IA)	Yes:	Claims	1-11
	No:	Claims	

2. Citations and explanations

see separate sheet

Reference is made to the following documents:

D1 WO-A-0196285
D2 WO-A-03041649

V. Reasoned statement with regard to novelty, inventive step or industrial applicability

Novelty

The present application refers to aminoacetonitrile derivatives of the general formula as referred to in claim 1 (claim 1), a pharmaceutical composition comprising them (claim 8) and their use in the treatment of cathepsin dependent conditions or diseases, e.g. osteoporosis, Paget's disease etc. (claim 9). The presently claimed compounds apparently inhibit the cathepsin activity, especially the cathepsin K activity.

None of the available prior art documents discloses a compound falling within the scope defined by the general formula. The subject-matter of claims 1, 8 and 9 as well as the dependent claims 2-7, 10 and 11 therefore appears to meet the requirement of Art. 33(2) PCT.

Inventive step

Aminoacetonitrile derivatives having similar structures for the same use are already known in the art, see D1 or D2. The presently claimed compounds are distinguished by the presence of a different substituent on the carbocyclic part, i.e. the substituent -D-E-R^5.

The problem to be solved by the present invention may therefore be considered as providing alternative compounds useful as cathepsin inhibitor.

The solution proposed in claim 1 of the present application cannot be considered as involving an inventive step (Article 33(3) PCT) for the following reasons.

To be considered inventive the technical problem must be solved over basically

the whole scope of the claims.
Claim 1 of the application refers to a very large general formula, while only a small part is supported by the explicitly prepared compounds. It should be noted that the application does not contain any biological data demonstrating the alleged effect, but for the purpose of this opinion, it has been assumed that at least the explicitly prepared compounds have been tested and found active.
However, without any data showing that the problem is solved over the basically the whole breath of the claims, no inventive step can be acknowledged for the subject-matter of claims 1, 2, 4, 7-11 (Art. 33(3) PCT).

The subject-matter of claims 3, 5 and 6, which appears to be supported by the examples, may be considered to meet the requirement of Art. 33(3) PCT.

Attention is drawn to the following point:
In order for a claim to compounds using a Markush formula to be regarded as uniform, the claimed compounds should have in common a structural moiety which is distinctive in view of the prior art. The structural moiety common to all the presently claimed compounds is the unit *carbocycle-C(=O)N-CR^{1}R^2-CN*. However, such a moiety is to be found in the compounds according to D1 or D2. The subject-matter of claims 1, 2, 4, 7-11 appears therefore to lack unity of invention.

Industrial applicability

There are no objections against the industrial applicability of the presently claimed subject-matter.

Further objections:

Claims 1, 2 and 7-11 are not supported by the description as required by Article 6 PCT, as their scope is broader than justified by the description and drawings. The reasons therefor are the following:
These claims refer to a very large amount of compounds while only a very small part is supported by the explicitly prepared examples. In addition to this, biological data demonstrating the alleged activity are not present.

The second compound on page 66 (claim 7) does not fall under the general formula of claim 1. This inconsistency leads to doubt concerning the matter for which protection is sought, thereby rendering the claims unclear, Article 6 PCT.

The embodiments of the invention described on page 12, lines 33 - page 17, line 9 (methods of treatment) do not fall within the scope of the claims. The same applies to the statement on page 25, lines 26-27 (prodrugs) and the embodiment mentioned on page 30, lines 18-23. These inconsistencies between the claims and the description leads to doubt concerning the matter for which protection is sought, thereby rendering the claims unclear, Article 6 PCT.
In this context it should also be noted that the term *prodrug* does not clearly define a compound, because it merely refers to the result to be achieved (Article 6 PCT). Furthermore, a claim to the use of a compound in medical treatment would not be recognized as industrially applicable by the EPO.

The terms "aryl" and "heteroaryl" (see claims) refer to completely aromatic and heteroaromatic residues. They do not include compounds whereby only part of the residue described as aryl or heteroaryl is meant to be aromatic as mentioned on page 29, lines 14 or 19. This inconsistency between the claims and the description leads to doubt concerning the matter for which protection is sought, thereby rendering the claims unclear, Article 6 PCT.

Claim 10 comprises all the features of claim 8 and is therefore not appropriately formulated as a claim dependent on the latter (Rule 6.4 PCT). The same applies for claim 11, which comprises all the features of claim 9.

The variable "□" mentioned on various pages of the description (see for example pages 35-40, 42, 45-47) has no meaning (Art. 6 PCT).

Contrary to the requirements of Rule 5.1(a)(ii) PCT, the relevant background art disclosed in the documents D1 and D2 is not mentioned in the description, nor are these documents identified therein.